# The Present and Future Global Burden of the Inherited Disorders of Hemoglobin

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**KEYWORDS**

• Genetic disease • Sickle cell disease • Thalassemias • Public health
• Newborn screening • Malaria selection • Consanguinity • Human migrations

**KEY POINTS**

- The global burden of the inherited disorders of hemoglobin is increasing and this is finally starting to be recognized.
- Global, regional, and national newborn and population estimates need to be regularly updated to account for health and demographic changes, and this relies on reliable contemporary epidemiologic data.
- The highest burden of the inherited disorders of hemoglobin is and will remain in sub-Saharan Africa for sickle cell disease and in Southeast Asia for the thalassemias, and better prevention and management policies are urgently needed.

## INTRODUCTION

The inherited disorders of hemoglobin represent the most common monogenic diseases. It has been estimated that around 7% of humans are carrying one of the mutations responsible for these disorders.[1] Although they have been extensively studied at the molecular and cellular level, epidemiologic data to assess the health burden of these disorders are often limited, particularly in regions of high prevalence, which are mostly found in tropical areas.[2] These neglected disorders are becoming an increasing health burden in low-, middle-, and high-income countries.[3] After a short description of the inherited disorders of hemoglobin, this article summarizes progress made toward better awareness and recognition of these disorders as a global health problem before presenting the main factors that influence their present and future burden, and discussing the strengths and limitations of existing estimates.

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## INHERITED DISORDERS OF HEMOGLOBIN

These disorders are classified into two main groups: the structural variants of hemoglobin and the thalassemias, which both follow an autosomal-recessive pattern of inheritance. Maps showing the distribution of each disorder are shown in **Fig. 1**.

### *Structural Hemoglobin Variants*

More than 1200 structural variants resulting mostly from single amino acid substitutions in the α- or β-globin chains have been identified.[4] Most of them have a limited geographic distribution and reached a low frequency. Nevertheless, the three polymorphisms described next are common and clinically significant.

#### *Hemoglobin S*

Hemoglobin S (HbS), also called sickle hemoglobin, is a structural variant of normal adult hemoglobin (HbA) caused by an amino acid substitution at position 6 of the β-globin chain (HBB c.20A > T; p.Glu6-Val). Carriers or heterozygotes (HbAS) are almost always asymptomatic, whereas homozygotes (HbSS) suffer from sickle cell anemia, which often leads to acute and chronic complications including vaso-occlusive crisis, acute chest crisis, or hemolytic crisis.[5] Because of its high level of protection against *Plasmodium falciparum* malaria, HbS was initially largely restricted to Africa, the Middle East, and parts of India.[6] Nowadays, this variant is found in almost every country, but particularly in the Americas, the Caribbean, and Europe following human diasporas (see **Fig. 1**A).[7]

#### *Hemoglobin C*

HbC is another structural variant of HbA caused by an amino acid substitution (HBB c.19G > A; p.Glu6Lys) occurring at the same position as HbS. Although carriers

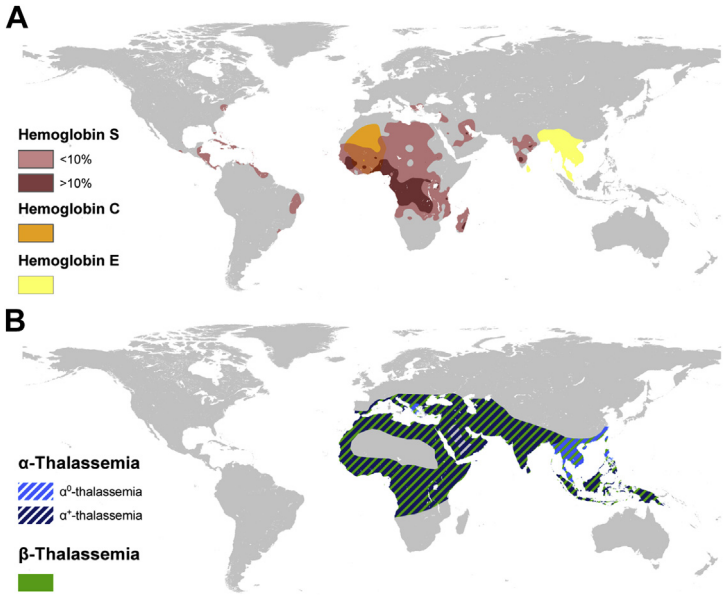


**Fig. 1.** Maps of the distribution of the inherited disorders of hemoglobin. (*A*) Structural hemoglobin variants. (*B*) Thalassemias. (*Adapted from* Refs.[7–9,61])